(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time;

(d) comparing the amount of product detected in (c) to the amount detected in (b) wherein an increase in the amount of product in step (c) as compared to the amount of product in step (b) indicates progression of said colon cancer and wherein a decrease in the amount of product in step (c) as compared to the amount of product in step (b) indicates a remission of said colon cancer. and thereby monitoring the progression of colon cancer in the patient.

REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the following remarks. Claims 80, 81, 83, and 84 have been canceled. Claims 79, 82, and 85 have been amended and new claims 86 and 87 have been added for purposes of clarity and to place this application in better condition for allowance and/or appeal. It is urged that support for all the above amendments and new claims may be found throughout the specification as originally filed and that none of these amendments or new claims constitutes new matter. Specifically, support for amplifying an expressed product in an RT-PCR reaction can be found, for example, on page 46, line 25 - page 47, line 27. With the above amendments, claims 79, 82, and 85-87 are pending. It should also be noted that the above amendments and claim cancellations are made without prejudice to prosecution of any or all subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

Rejections under 35 U.SC. § 112, first paragraph (enablement)

Claims 79-84 stand rejected as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to

which it pertains to make and/or use the claimed polynucleotide sequences. More specifically, the Examiner contends that the specification does not teach what differences in expression are encompassed by the vague terms "overexpression" versus "low level overexpression" of SEQ ID NO:21. The Examiner further asserts that Grotzinger *et al.* teaches that L1-cadherin is expressed in the large intestine of healthy individuals (i.e. normal colon) and thus that it is unclear whether SEQ ID NO:21 is a colon tissue-specific transcript expressed in both colon tumor and normal colon tissue. The Examiner also asserts that the specification has provided no teaching that mutants, homologs, and variants of SEQ ID NO:21 are overexpressed in colon tumor tissue. The Examiner also contends that the specification lacks guidance as to whether colon cancer can be detected by detecting the overexpression of SEQ ID NO:21 in various biological samples, in particular in blood. Additionally, the Examiner believes that the specification does not provide evidence of a correlation between an increase in expression of SEQ ID NO:21 and progression of colon cancer. The Examiner further alleges that the specification does not provide evidence that the **protein** expressed by SEQ ID NO:21 is elevated at least two fold in colon tumor tissue as compared to normal tissue. The Examiner also believes that the specification does not teach that SEQ ID NO:21 is a fragment of L1-cadherin. Lastly, the Examiner alleges that the specification does not teach an acceptable predetermined cut off value and therefore, the skilled artisan must determine that value. Thus, the Examiner alleges that it would require undue experimentation on the part of the skilled artisan to practice the claimed invention.

Applicant respectfully traverses the rejection on the following grounds.

Applicant wishes to stress that he is in agreement with the Examiner that SEQ ID NO:21 is indeed a **colon tissue**-specific transcript and not a **colon tumor**-specific transcript, as was discussed in response to the Office Action of June 5, 2001. Furthermore, Applicant submits that the skilled artisan would readily recognize this given the instant disclosure, in particular on page 53, lines 7 - 10, where the specification states that SEQ ID NO:21 showed "low level overexpression in 3/6 **normal colon tissues** tested" (emphasis added). Given this overexpression in normal colon tissue, the skilled artisan would appreciate that SEQ ID NO:21 is a colon-specific transcript, as noted by

the Examiner and shown in the art, and not a colon tumor-specific transcript. As such, the skilled artisan would recognize that the difference in expression between **colon tumor** tissue and **normal colon** tissue is not relevant for the instant invention. Rather, it is the tissue-specificity, and the relative expression of SEQ ID NO:21 in colon tissue versus normal tissues, other than normal colon, that is pertinent. In this regard, the skilled artisan would therefore recognize that the difference between "overexpression" and "low level overexpression" observed in colon tumor and normal colon tissue, respectively, is not relevant. Rather, the skilled artisan would readily understand given the guidance in the specification, that SEQ ID NO:21 should be overexpressed by at least 2-fold in colon tumor tissue as compared to normal tissue **other than normal colon**. This guidance can be found, for example on page 52, lines 10 - 11 or on page 14 where "colon tumor protein" is defined as a protein that is expressed in colon tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue. Applicant wishes to note that this definition does not stipulate that the colon tumor protein be 2-fold overexpressed as compared to the level of expression in a normal **colon** tissue.

With regard to the contention that the specification lacks guidance as to whether colon cancer can be detected by detecting the overexpression of SEQ ID NO:21 in blood, Applicant respectfully notes that the specification teaches that no significant levels of expression of SEQ ID NO:21 were detected in a panel of normal tissues, including kidney, lung, liver, brain, heart, esophagus, small intestine, stomach, pancreas, adrenal gland, salivary gland, resting PBMC, activated PBMC (Applicant notes that PBMC are found in blood), bone marrow, dendritic cells, spinal cord, blood vessels, skeletal muscle, skin, breast and fetal tissues. Thus, Applicant has shown that SEQ ID NO:21 cannot be detected in cells in the blood, or any other normal tissue tested. Therefore, Applicant asserts that the skilled artisan would recognize that detection of expression of SEQ ID NO:21 in any of these tissues, including blood, would therefore signify the presence of colon **cells**, *i.e.* the presence of metastatic colon tumor cells in the normal tissues being tested. Furthermore, Applicant urges that given the guidance in the specification (for example, on page 46, line 25 - page 47, line 27) and the general level of

knowledge in the diagnostic arts, the skilled artisan would readily understand how to detect even the rarest of cells in any of the above tissues. Moreover, Applicant respectfully submits that there would be a more than reasonable expectation, in view of the colon-specific expression profile identified in the instant disclosure for SEQ ID NO:21, that any of a number of biological sample types could be employed in the claimed methods for detecting colon cancer in a patient, including blood.

With regard to the contention that the specification does not provide evidence of a correlation between an increase in expression of SEQ ID NO:21 and progression of colon cancer Applicant urges that the pending claims recite that an increase in **the amount of oligonucleotide that hybridizes** in step (d) as compared to **the amount of oligonucleotide that hybridizes** in step (c) indicates progression of colon cancer, or in new claim 87, wherein an increase in **the amount of product** in step (c) as compared to **the amount of product** in step (b) indicates progression of said colon cancer. Therefore, Applicant submits that the skilled artisan would readily recognize that the claims do not require a correlation between an increase **in expression** of SEQ ID NO:21 and progression of colon cancer. Rather, Applicant submits that the skilled artisan would recognize that the increase in the amount of oligonucleotide that hybridizes or the amount of amplified expressed product could signify, for example, an increase in the number of metastatic colon tumor cells present in a given sample thereby signifying the progression of cancer. Therefore, a correlation between an increase in expression of SEQ ID NO:21 *per se* and progression of colon cancer is not necessary.

The Examiner further alleges that the specification does not provide evidence that the **protein** encoded by a polynucleotide comprising SEQ ID NO:21 is elevated at least two fold in colon tumor tissue as compared to normal tissue. Applicant submits that those of skill in the art recognize that expression of mRNA is a first and necessary step in the expression of a polypeptide and that there is a reasonable expectation of correlation between mRNA expression and protein expression. Therefore, there is a reasonable expectation that the expression of cDNA comprising the cDNA of SEQ ID NO:21, would correlate with the expression of a protein encoded by a cDNA comprising the cDNA of SEQ ID NO:21 (i.e. L1-cadherin). Furthermore, Applicant

submits that the Examiner has not cited any evidence supporting the assertion that a polynucleotide comprising SEQ ID NO:21 is not translated into protein. As is clarified by the attached Declaration of Dr. Gary Fanger, immunohistochemical analysis of expression of L1-cadherin (encoded by a polynucleotide comprising SEQ ID NO:21) in colon tumor and normal colon samples shows that this protein, as expected based on the mRNA expression profiles described in the instant specification, is indeed expressed in colon tissue. Furthermore, confirming what is described in the specification, C888P (L1-cadherin, encoded by the full-length sequence comprising SEQ ID NO:21) is detected by immunohistochemistry in both normal colon and colon tumor tissue but is not detected in a variety of other normal tissues. Thus, as described in the specification as filed, the protein encoded by the full-length polynucleotide comprising SEQ ID NO:21 (L1-cadherin) is overexpressed in colon tumor tissue and normal colon tissue as compared to other normal tissues.

The Examiner also believes that the specification does not teach that SEQ ID NO:21 is a fragment of L1-cadherin. Applicant maintains that the skilled artisan would readily appreciate in light of the guidance provided in the application, that SEQ ID NO:21 represents a fragment of L1-cadherin. Applicant urges that the skilled artisan would readily recognize that all of the differences between SEQ ID NO:21 and the publicly available sequence of L1-cadherin (when SEQ ID NO:21 is compared to Genbank Accession Number NM_004063, a single n at nucleotide 1755 and an insertion of an adenine nucleotide at position 2009), can be attributed to sequencing errors. For the convenience of the Examiner, Applicant submits herewith an additional Declaration of Dr. Susan Harlocker clarifying this issue. Therefore, given the guidance in the specification and the level of skill in the art, the skilled artisan would readily conclude that SEQ ID NO:21 is a fragment of L1-cadherin.

The Examiner alleges that the specification does not teach an acceptable predetermined cut off value and therefore, the skilled artisan must determine that value. Applicant respectfully traverses this rejection and submit that an artisan skilled in the diagnostic arts would have no difficulty identifying a suitable negative or normal control value, *e.g.*, a "predetermined cut-off value", in the context of the currently claimed

. A specific predetermined cut-off value is simply not needed, either in the ıtion or in the claims, when the skilled artisan would fully appreciate the routine ɔf identifying a suitable value for the assay being employed. Moreover, ıt's specification indeed offers illustrative guidance on this point, for example, in ɡraph bridging pages 44 and 45, where it is disclosed that, in one embodiment, off value for the detection of a cancer is the average mean signal obtained when ɔbilized antibody is incubated with samples from patients without the cancer. In a sample generating a signal that is three standard deviations above the ıined cut-off value is considered positive for the cancer." The specification s, at page 45, lines 1-3, that in another embodiment, "the cut-off value is ed using a Receiver Operator Curve, according to the method of Sackett *et al.*, Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 106-7." Thus, in view of Applicant's disclosure of illustrative means for ıg a suitable "predetermined cut-off value", and further in view of the level of he diagnostic arts, it is respectfully submitted that a skilled artisan can readily a "predetermined cut-off value" for use in the context of the currently claimed ı using only routine and art-recognized techniques.

Lastly, the Examiner asserts that the specification has provided no that mutants, homologs, and variants of SEQ ID NO:21 are overexpressed in nor tissue. Without acquiescing to the Examiner's rejection, Applicant has the claims without prejudice, to remove recitation of sequences having 90% ɔ SEQ ID NO:21, obviating this ground for rejection.

In light of the above arguments, Applicant respectfully submits that the ɔlaims are fully enabled by the present specification as required by 35 U.S.C. § t paragraph, and respectfully request reconsideration and withdrawal of the

Rejections under 35 U.SC. § 103

Claim 85 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Dantzig *et al.* (U.S. Patent 5,710,018) in view of Reeves *et al.* (U.S. Patent 6,312,891) and Ahern, H.(www.the-scientist.library.upen.edu; 1995, pages 1-5).

Applicant respectfully traverses this rejection and submits that the combined primary, secondary, and tertiary references, taken for what they teach as a whole, do not teach or suggest the claimed invention. Therefore, Applicant submits that the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing.

Specifically, while Dantzig *et al.* teach a sequence comprising SEQ ID NO:21, nowhere does Dantzig *et al.* teach that the mRNA or protein encoded by a sequence comprising SEQ ID NO:21 is over-expressed in any tumor tissue, let alone colon tumors, as compared to any normal tissue. Dantzig *et al.* is simply a description of the sequence encoding a mammalian influx peptide transporter. While Applicant agrees with the Examiner that the reference generally states that probes based on the sequence may be used to identify clones that contain DNA encoding the influx peptide transporter, nowhere does the cited reference discuss colon cancer or expression levels of the sequence in normal or tumor tissues of any kind. Therefore, it would not have been obvious to the skilled artisan that this sequence could be used to detect or monitor colon cancer. Applicant submits that the teachings of Reeves *et al* and Ahern do not overcome the deficiencies of Dantzig *et al.* and therefore, these three references, taken for what they teach as a whole, do not teach or suggest the claimed invention.

Nevertheless, without acquiescing to the Examiner's rejection, to more particularly point out Applicant's invention, Applicant has amended the claim to recite a diagnostic kit for use in the detection of colon cancer. Thus, Applicant respectfully submits that the rejection has been obviated and may be properly withdrawn. Applicant respectfully submits that following withdrawal of the rejection under 103(a), claim 85 is in condition for allowance.

Double Patenting

Claim 85 stands provisionally rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claim 15 of copending Application No. 09/922,217 in view of Reeves *et al.* and Ahern, H. Applicant respectfully requests that the Office hold this rejection in abeyance until the claims are otherwise found to be allowable.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**."

Favorable reconsideration and allowance of the pending claims are respectfully requested. The Examiner is invited to contact the undersigned with any questions, concerns or suggestions pertaining to this communication.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

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Enclosures:

Postcard
Declaration of Gary Fanger, Ph.D.
Declaration of Susan Harlocker, Ph.D. (Figure 1 attached thereto)

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 80, 81, 83, and 84 have been canceled.

New claims 86 and 87 have been added.

Claims 79, 82, and 85 have been amended as follows:

79. (Amended) A method for determining the presence of colon cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide that hybridizes under moderately stringent conditions to a polynucleotide sequence comprising ~~a sequence selected from the group consisting of:~~

~~(i)~~SEQ ID NO:21~~; and~~

~~(ii)sequences having at least 90% identity to SEQ ID NO:21~~;

(c) detecting in the sample an amount of oligonucleotide that hybridizes to the polynucleotide; and

(d) comparing the amount of oligonucleotide that hybridizes to the polynucleotide to a predetermined cut-off value, wherein an increase in the amount of oligonucleotide that hybridizes to the polynucleotide as compared to the predetermined cut-off value indicates the presence of cancer in the patient.

82. (Amended) A method for monitoring the progression of colon cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide that hybridizes under moderately stringent conditions to a polynucleotide sequence comprising ~~a sequence selected from the group consisting of:~~

SEQ ID NO:21~~; and~~

~~sequences having at least 90% identity to SEQ ID NO:21~~;

(c) detecting in the sample an amount of oligonucleotide that hybridizes to the polynucleotide;

(d) repeating steps (a)-(c) wherein the biological sample is obtained from the patient at a subsequent point in time; and

(e) comparing the amount of oligonucleotide detected in (d) to the amount detected in (c) wherein an increase in the amount of oligonucleotide in step (d) as compared to the amount of oligonucleotide in step (c) indicates progression of said colon cancer and wherein a decrease in the amount of oligonucleotide in step (d) as compared to the amount of oligonucleotide in step (c) indicates a remission of said colon cancer.

85. (Amended) A diagnostic kit for use in the detection of colon cancer, comprising:

(a) at least one oligonucleotide that hybridizes under moderately stringent conditions to a polynucleotide sequence comprising a sequence selected from the group consisting of:

(i) SEQ ID NO:21, and

(ii) sequences having at least 90% identity to SEQ ID NO:21; and

(b) a reporter group for use in a ~~polymerase chain reaction or~~ hybridization assay.